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Svanberg, Katarina; Bendsöe, Niels; Axelsson, Johan; Andersson-Engels, Stefan; Svanberg, Sune

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Photodynamic therapy: superficial and interstitial illumination

Katarina Svanberg
Lund University
Department of Oncology
221 00 Lund, Sweden

Niels Bendsoe
Lund University
Department of Dermatology
221 00 Lund, Sweden

Johan Axelsson
Stefan Andersson-Engels
Sune Svanberg
Lund University
Department of Physics
221 00 Lund, Sweden

Abstract. Photodynamic therapy (PDT) is reviewed using the treatment of skin tumors as an example of superficial lesions and prostate cancer as an example of deep-lying lesions requiring interstitial intervention. These two applications are among the most commonly studied in oncological PDT, and illustrate well the different challenges facing the two modalities of PDT—superficial and interstitial. They thus serve as good examples to illustrate the entire field of PDT in oncology. PDT is discussed based on the Lund University group's over 20 yr of experience in the field. In particular, the interplay between optical diagnostics and dosimetry and the delivery of the therapeutic light dose are highlighted. An interactive multiple-fiber interstitial procedure to deliver the required therapeutic dose based on the assessment of light fluence rate and sensitizer concentration and oxygen level throughout the tumor is presented. [DOI: 10.1117/1.3466579]

Keywords: photodynamic therapy; lasers in medicine; biomedical optics.

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1 Background—Cancer and Its Treatment

The incidence of tumor diseases is growing slowly in almost every country in the world. In the developed countries, approximately one in three people will be diagnosed during their life as having one or more malignant tumors. With an aging population, this figure will increase as age is the most important factor in developing malignant tumors. Cancer is thus defined as one of the world's endemic diseases. Cancer is the second largest cause of death in the Western world after cardiovascular disease. From a historic perspective, tumors are described in ancient Indian and Chinese scripts and Egyptian papyrus rolls dating back to 2000 B.C. Tumors can also be seen in some very old paintings as well as in mummies and paleontological findings from both the Old and the New World. Burning sticks, herbal decoctions, and ointments were used in those days to treat tumors. Surgery was the dominant form of treatment until the beginning of the 20th century, when ionizing radiation was discovered and became another treatment option. Röntgen[1] published a paper in 1896 called "Über eine neue Art von Strahlen" ("On a New Kind of Rays") and, as the first Nobel laureate in physics, received the Nobel Prize in 1901 for this discovery. A few years later, the new treatment modality was already introduced in specialized hospitals in Germany, England, and France; international conferences within the new field were organized; and fascinating results presented.

2 Phototherapy

Phototherapy (PT) and photochemotherapy (PCT), as well as ionizing radiation, are treatment modalities related to physical phenomena arising from the interaction of electromagnetic irradiation with biological tissue. In this review, we consider electromagnetic radiation in the visible range, i.e., light. The difference between PT and PCT is that in the latter case a photosensitizing agent is administered before exposure to light. Both therapies have a long history and date back to the ancient Greek, Egyptian, and India civilizations. In Egypt and India, psoralen plants were used in combination with sunlight for the treatment of vitiligo (white/hypopigmented spots in the skin), representing the first examples of the use of PCT in humans, while the ancient Greeks practiced full-body sun exposure, later termed heliotherapy. In modern history, a pioneer in the field of PT is Niels Finsen, who was awarded the Nobel Prize in 1903 for his discoveries using light in the treatment of cutaneous tuberculosis.[2] Finsen is often referred to as the father of modern phototherapy, a field that is still relevant for the treatment of dermatological conditions such as psoriasis and certain other types of dermatitis. Another example of PT is the treatment of juvenile jaundice utilizing UV light.[3] A new and interesting application of PT is in psychiatry, where encouraging results have been achieved in the treatment of seasonal affective disorder, which is relatively common in the Nordic countries due to the dark winter season.[4] Depression resulting from this disorder is associated with low levels of the neurotransmitter serotonin in the brain. Exposure to light increases these levels, thus leading to alleviation of the symptoms.[5]

Photodynamic therapy (PDT) is a kind of PCT that relies on the presence of oxygen in the tissue, and is a local treatment modality with the potential of being selective. A so-called sensitizing agent, which is taken up and retained in the tumor, is administered prior to exposure to light. PDT was

Address all correspondence Katarina Svanberg, Lund University, Department of Oncology, Lund, 221 85, Sweden. Tel: 46-46-222-4048; Fax: 46-46-222-3177; E-mail: Katarina.Svanberg@med.lu.se.

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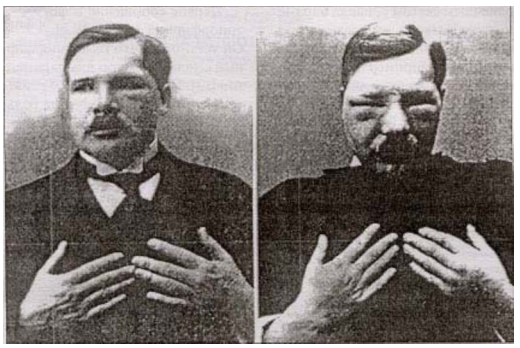

(a) (b)

Fig. 1 Photograph of F. Meyer-Betz before and after injecting himself with 200 mg of Hp leading to extensive skin photosensitization (from Ref. 8).

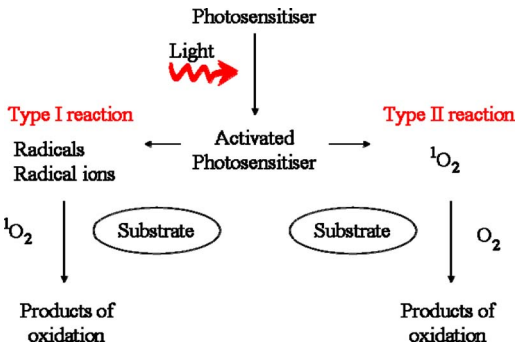

Fig. 2 Three components of importance for photodynamic therapy: the PS, light, and molecular oxygen.

first demonstrated by a medical student, Oscar Raab, in 1898 when he discovered the toxic action of acridine on paramecia (a unicellular microorganism) in conjunction with ambient light.[6] The student worked in the laboratory of Herman von Tappenier in Munich who reported in 1904 that the process Raab had described was dependent on oxygen, and von Tappenier was the first to use the term photodynamic therapy to describe the phenomenon of oxygen-dependent photosensitization.[7] Von Tappenier was also the first to perform PDT on humans with skin cancer, cutaneous lupus erythematosus (an inflammatory rheumatic disease), and genital condylomas (virus-induced warts) using eosin as a photosensitizing agent.

The physical properties of the sensitizer hematoporphyrin (Hp) were first described in 1908, and its biological activity was demonstrated a few years later, in 1913, when a German physician, F. Meyer-Betz, injected himself with 200 mg of Hp and remained sensitive to light for 2 months[8] (Fig. 1). This sensitization was similar to that of patients suffering from the inherited disorder porphyria, resulting from the deficiency of certain enzymes in the heme biosynthesis pathway. Various porphyrins and their precursors accumulate in the skin of these patients, and they thus show the same type of skin sensitization as that resulting from the administration of Hp. The term porphyrin comes from the Greek word "purphura," which means purple pigment and refers to the fact that these patients have purple/brown-colored urine.

The selective retention of hematoporphyrins in tumor tissue was first observed by Policard[9] in 1924, and that of various porphyrins in the same type of tissue in 1948 by Figge and Weiland.[10] The use of PDT utilizing derivatives of hematoporphyrin (hematoporphyrin derivative, HpD) was introduced by Lipson et al.[11] during the 1960s, followed by Bonnett et al.[12] who used a mixture of oligomeric porphyrins. The technique was improved by Dougherty, who refined the porphyrin mixture, mainly by linking it with ester and ether bridges, and performed research into the potential of the PDT technique. Dougherty was instrumental in introducing the treatment modality into clinical use.[13]

Many review papers on PDT have already been published (e.g., Refs. 14–16). In this paper, our aim is to provide a clinical prospective and compare the challenges of superficial and interstitial PDT. We have chosen to exemplify these different modalities of PDT by two clinically important applications: the treatment of skin cancer as an example of thin tumors that can be treated with broad-beam illumination from the surface, and the eradication of prostate cancer, requiring interstitial light delivery. These two modalities also constitute two of the most commonly studied forms of PDT in oncology, further motivating this choice. The dosimetry requirements are very different in these two cases, as described in the following, illustrating an important difference in the approaches.

3 Phototoxicity

Three components are required to cause phototoxicity in targets such as tumors: a photosensitizer (PS), light of the appropriate wavelength, and the substrate. The process of PDT is illustrated in Fig. 2.

1. A PS or a prodrug (precursor) to a PS is administered (systemically or locally) to the subject and allowed to accumulate in the malignant cells (preferentially selectively). The role of the PS is to absorb the energy of the light photons and then transfer it to the substrate.

2. The light must be of a wavelength appropriate to the absorption peaks in the spectrum of the PS. Some PS agents have more than one absorption peak (usually in the blue/green as well as in the red wavelength region), and the penetration depth into the tissue will vary depending on which of these wavelengths is used.

3. The substrate is the oxygen in the tissue. When the oxygen molecules absorb the excess energy of the PS resulting from light exposure, singlet oxygen is formed, which initiates the chemical destruction of the tumor cells.

Cell death can be caused immediately by PDT, by the rupture of the cell membrane, or can occur after a number of days or weeks through the induction of damage to the vascular system or by cell necrosis and apoptosis due to the involvement of the immune system. Rupture of the cell membrane results when the PS used is an oligomer. These are lipophilic and therefore attach to the cell membrane. In the equilibrium between oligomers and monomers, some of the bound oligomers are transformed to hydrophilic monomers. When these are formed, the PS can be released from the membrane to the interior of the cells, where it becomes attached to the mitochondria or the lysosomes. This disrupts the respiration of the cell, leading to its death.

4 Procedure for PDT

The principle of PDT in the treatment of cancer is quite simple. However, certain important parameters must be taken into consideration to optimize the outcome of the therapy. Examples of these are

1. selection of the PS: absorption wavelength, drug dose for the tumor type in question, and drug-light time interval between PS administration and light irradiation (minutes to days)
2. irradiation mode (superficial or interstitial): total light fluence or light dose delivered (in joules per square centimeter), light fluence rate or light dose rate (in watts per square centimeter), light fractionation, and light source

4.1 *Photosensitizers*

An ideal photosensitizer for PDT should be:

1. nontoxic in the absence of light
2. highly efficient at absorbing light energy and transferring it to the substrate
3. able to absorb light at "longer" wavelengths, preferably above 600 nm to enable increased light penetration in tissue
4. accumulated selectively within tumors (high tumor:normal tissue ratio)
5. cleared rapidly from the normal surrounding tissue and organs at risk

Considerable effort has been devoted to the search for the ideal PS. However, it is unlikely that a single sensitizer will be optimal for all types of tumors. HpD is sometimes called the first-generation PS, and others second-generation PSs. One of these other agents, aminolevulinic acid (ALA), is a precursor of a PS. ALA is transformed into an active PS in the heme cycle in the cells. PSs are chemical substances that absorb light in the red wavelength range (Table 1). A wavelength shift from 630 to 720 nm corresponds approximately to a doubling of the light penetration depth, i.e., the depth at which the light is attenuated to 37% $(1/e)$ of its initial value. In terms of millimeters, this corresponds to a change from about 3 to about 6 mm. This means that thin tumors can be efficiently treated with these PSs using superficial illumination. For thicker tumors or tumors deeper in the body interstitial light irradiation must be applied. This is usually done by transmitting the light through optical fibers inserted into the bulk of the tumor.

The time interval between the administration of a PS and light illumination varies depending on the PS. For HpD it is usually a few days. When using one of the newer sensitizers, for example, a bacteriochlorophyll called Tookad, it is only minutes, since the action is mainly on the endothelial cells in the vessels. An important discovery was made when it was shown that the PS could be applied topically for the treatment of skin cancer and precancerous cells.[17,18] In this way, it is possible to avoid long-term sensitization of the whole of the patient's skin, which results from systemic administration of the PS. Photosensitivity is also a side effect of many other pharmaceuticals given to patients in daily practice. These include some antibiotics (tetracyclines and sulfonamides), nonsteroidal anti-inflammatory drugs (e.g., naproxen, ketoprofen, and ibuprofen), diuretics (hydrochlorothiazide), and some neuroleptics. Photosensitivity may also be initiated by the use of some fragrances (e.g., musk perfume) and aspirin. The reversible clinical effects of these drugs are quite similar to those of systemically administered PSs, i.e., a dry, bumpy, or blistering rash on the skin.

Table 1 Different sensitizers with the major absorption peak in the red part of the wavelength spectrum. The names in square brackets are the registered trade names.

Photosensitizer	Wavelength of Red Absorption Peak (nm)
Hematoporphyrin derivative (HpD), [Photofrin]	630
Delta-aminolevulinic acid (ALA), [Metvix, Levulan]	635
Meso-tetra-hydroxyphenyl-chlorin (mTHPC), [Foscan]	652
Tin etiopurpurin [Pyrlytin]	660
Phthalocyanine	675
Benzoporphyrin derivative (BPD), [Verteporfin, Visudyne]	690
Lutetium texaphyrin [Lutrin]	732
Bactriochlorophyll [Tookad]	760

Several important parameters must be taken into account concerning the light activation of the PS. Most PSs have several light absorption peaks. The absorption peak in the UV or blue part of the spectrum (the Soret band) is usually higher. However, a red absorption wavelength is usually chosen for the treatment of tumors due to its deeper penetration. As PS agents can also be used for tumor detection, the UV or blue bands are utilized to generate red fluorescence. This technique has shown great potential for early tumor detection and visualization of shallow lesions. The use of laser-induced fluorescence (LIF) in conjunction with PDT for tumor delineation and treatment guidance provides an additional tool for improved therapy.

4.2 *Light Sources*

Monochromatic lasers were initially the natural choice for PDT. However, before practical diode lasers became available, the systems were complicated and required the help of physicists. The first lasers used in PDT were Au- or Cu-vapor lasers, and argon-ion-pumped dye lasers emitting in the red spectral region. Another possibility emerged with the frequency-doubled neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, emitting light at 532 nm, and pumping a dye laser. Solid state diode lasers were introduced in the clinic in the late 1990s. The advantage of using lasers in PDT is the possibility of transmitting the light through optical fibers, thus providing the option of treating tumors in hollow organs, such as the urinary bladder, the bronchus, the intestines, and the esophagus. For superficial illumination, for example the skin, female genital tract, or the oral cavity, an array of light-

emitting diodes (LEDs) is suitable for the task. As PSs do not have very narrow absorption features, LEDs with a bandwidth of approximately 10 to 25 nm are fully acceptable as a treatment light source for superficial PDT.

5 Photodynamic Therapy as a Clinical Procedure

PDT is a local treatment modality and shows some very attractive characteristics as a clinical procedure in comparison with other treatment modalities. PDT is characterized by:

1. selective action on sensitized cancer/precancerous tissue
2. possibility of being repeated (in contrast to ionizing radiation)
3. no accumulation of toxicity
4. no or extremely low mutagenic potential
5. fast healing with good cosmetic results
6. retained organ function

6 Superficial PDT in Skin Lesions

Skin cancer is the most common of all human malignancies. It is increasing rapidly due to an increase in exposure to UV light, resulting from the use of sun beds, and longer leisure periods with holidays in hot countries, as well as an aging population. All classic skin cancers, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma, are related to sun exposure. Some precancerous skin lesions are also related to exposure to UV light, such as actinic keratosis and Mb Bowen (squamous cell carcinoma *in situ*). Several benign, premalignant, and malignant lesions in the skin are suitable for PDT, as listed next.

1. Benign lesions include psoriatic lesions, acne vulgaris, verucca vulgaris, and lichen ruber (mucosal).
2. Potentially malignant lesions include actinic keratosis, Mb Bowen (squamous cell carcinoma *in situ*) and cutaneous lymphoma.
3. Malignant lesions include basal cell carcinoma, squamous cell carcinoma, Mb Paget, and extramammary Mb Paget (adenocarcinoma *in situ*).

The only primary skin malignancy that is currently not a candidate for PDT is malignant melanoma, as this type of tumor must be surgically removed for extensive histopathological examination, for prognostic evaluation, and for continued management. A single treatment session is usually sufficient for lesions with a thickness of up to 3 mm. Thicker lesions can be retreated after follow-up, or pretreated, e.g., with curettage. This means that a layer of the tumor is removed surgically and PDT is performed to the tumor bed.

Due to the fact that skin cancer is common, the cost of treatment is substantial. Statistics for Sweden, which has a population of approximately 9 million, show[19] that the cost amounts to 125 million Euro/year. As there are several options for treating skin malignancies, such as surgery, cryosurgery, ionizing radiation, and topical cytotoxic drugs, the method should be chosen carefully to ensure optimal outcome. PDT has an important role in certain niches of skin malignancies, such as large tumors (diameter >3 cm); multiple tumor locations; sensitive locations (pretibial, periocular, outer ear); recurrent tumors; earlier radiation treatment; and high demands on cosmetic outcome (face, neck, and chest).

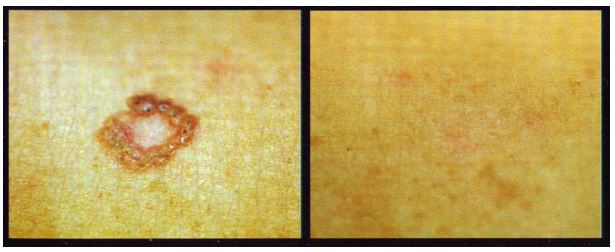

Fig. 3 Basal cell carcinoma treated with ALA-induced PDT, before (left) and about 3 months after (right) the treatment.

In the first clinical applications of PDT to skin malignancies PSs were administered systemically.[20–23] The introduction of topical application of ALA led to significant advances in PDT, hailing the start of a new era. ALA is a naturally occurring 5-carbon, straight-chain amino acid. It is highly soluble in water and can thus be mixed in water-based creams for topical application. ALA is the first step in the biosynthesis of heme in human cells, and when administered to an organism, it enters the endogenous heme cycle in the cells. Protoporphyrin IX (PpIX) is formed following many enzymatically driven steps. PpIX is, in contrast to ALA, a very potent PS. There is a transient buildup of PpIX in malignant cells partly due to lower levels of the enzyme ferrochelatase, which transforms PpIX to heme. The process can be followed by LIF, and the optimal time for irradiation is chosen when the normal:tumor tissue ratio is high. LIF can also be used for tumor delineation and target definition to minimize the risk of missing parts of the tumor not visible to the naked eye, thereby increasing the chances of successful treatment.

Malik and Lugaci were the first to discover ALA-induced PDT action in human leukemia cells.[17] The full clinical treatment potential was recognized by Kennedy et al.,[18] and Kennedy and Pottier,[24] who were the first to use topical ALA administration when treating skin malignancies in humans, and presented the first results in 1990. The Lund University group started clinical use of ALA-PDT for the treatment of skin tumors in 1991, and it is now a routine modality for treating certain skin malignancies.[25,26] As an example of the application of ALA-induced PDT, a basal cell carcinoma is shown in Fig. 3, before and about 3 months after treatment. The results are very similar as those with other treatment modalities, with a cure rate of approximately 85%, but the cosmetic results are better than with other methods. The only modality that results in a lower recurrence rate is Mohs surgery, which is an interactive, time-consuming modality, often resulting in the removal of very large areas of skin.[27]

For PDT of, e.g., skin malignancies a light dose of 60 J/cm^2 is commonly applied through surface illumination. The irradiance is usually kept below 150 mW/cm^2 so as not to heat the tissue. If higher irradiances are applied, hyperthermic effects may occur that can affect the result of PDT, causing the induction of fibrosis, organ dysfunction, with loss of tissue elasticity and impaired cosmetic results.[28]

The dosimetry for PDT of skin cancer is often very simple, and there is no real need for complicated calculations. The

reasons for this are that the lesions are usually very thin, and there are no critical organs at risk nearby, therefore, the exact position of the treatment boundary is not very critical. Superficial illumination yields a fairly low gradient of the fluence rate of the light inside the tumor, making it relatively simple to deliver sufficient light to the entire lesion. High selectivity in the uptake of the PS usually also helps spare the healthy surrounding tissue. The latter is in particular true for topically applied ALA-induced PpIX, which has a very high selectivity.

7 Interstitial PDT for Prostate Cancer

Prostate cancer is the most common malignant tumor in men after skin cancer. The prevalence of both cancers is strongly correlated with age. The first signs of prostate cancer are often urological symptoms and an increase in the PSA level (prostate specific membrane antigen), which is overexpressed in prostate cancer. An elevated PSA value is a diagnostic indicator of a potential problem, but can also be related to benign disorders, such as prostatitis or benign hyperplasia of the gland.

Common treatment modalities for prostate cancer include surgery, irradiation with ionizing radiation externally or internally, and hormone therapy. Short-range internal ionizing therapy, or brachytherapy, can be administered by the insertion of sealed needles containing iridium-192 (high-dose-rate brachytherapy) for a short period (5 to 15 min) or by permanent implantation of ionizing iodine-125 or palladium-103 seeds (low-dose-rate brachytherapy). Both these modalities are associated with undesirable side effects such as, e.g., incontinence, erectile dysfunction, and rectal wall irritation with bleeding. Thus, it is highly desirable to develop individualized treatment based on PDT.

PDT of the prostate was first reported by Windahl et al.[29] in 1990, who successfully treated two patients with localized tumors using Photofrin®. The safety and feasibility of using ALA-induced PpIX for PDT of prostate cancer were investigated more than a decade later.[30]

PDT mediated by another drug [meso-tetra(hydroxyphenyl)chlorin (mTHPC, Foscan®)] of the prostate was reported by Nathan et al.[31] at University College London in patients with local recurrence after radiotherapy (biopsy proven). The same group continued work on mTHPC-PDT applied to untreated local prostate cancer in six patients.[32] Magnetic resonance imaging (MRI) examinations showed patchy areas with reduced contrast uptake in some patients. Others had more distinct features of devascularization, potentially indicating necrosis. The volume of the prostate increased by approximately 30%, due to edema and inflammation within the first week after treatment. The volume then decreased to about 30% of the baseline volume 2 to 3 months posttreatment. Reported complications following PDT were irritative urinary voiding symptoms, which were resolved after 4 months.

Other studies, in which Lutex® was administered to patients with localized recurrent prostate cancer after radiotherapy, were performed at the University of Pennsylvania.[33,34] The primary goal of the trial was to assess the maximally tolerated dose of Lutrin-PDT using 732-nm treatment light. The time between drug administration and the commencement of treatment varied between 3 and 24 h. A wide range of investigations were carried out, including measurements of the optical properties of the prostate gland,[35] fluorescence spectroscopy of the PS, (Ref. 36) and optical assessment of tissue oxygenation.[37] The measurements were performed using translatable spherical isotropic fiber optic light diffusers in which the light fluence rate could be measured directly. The optical measurements performed before, during, and after treatment all indicated substantial heterogeneity of the optical properties of the prostate and accumulation of the PS. Tissue oxygenation was relatively constant in each patient but the total hemoglobin concentration decreased during treatment. The conclusion of the study was that although the mild, transient complications make Lutrin PDT an attractive alternative to conventional prostate cancer therapy, the optical heterogeneity of the prostate gland must be taken into account to ensure correct light delivery. In a subsequent publication by the same group, short- and long-term effects on PSA levels were described in relation to the PDT dose.[38] The PDT dose was defined as the product of the PS concentration, measured pretreatment *ex vivo*, and the *in situ* measured light dose. Patients receiving high-dose PDT experienced a longer delay (82 days) to the time after treatment when the PSA level began to increase irreversibly than low-dose PDT patients (43 days). This group has also developed pretreatment dosimetry software intended to optimize parameters such as cylindrical fiber position and length, as well as irradiation power, to tailor the emitted treatment light according to a predefined dose plan.[39]

Trachtenberg et al.[40,41] at the University of Toronto reported on vascular targeted photodynamic therapy (VTP), using escalating drug doses of the photosensitizer WST09. Spherical isotropic probes were utilized for fluence rate measurements at selected sites.[42] Complete response was achieved in 60% of the patients who received high-dose VTP based on 1-week post-VTP MRI investigation, which showed avascular areas.[43] Biopsies from these patients showed no viable cancer after 6 months. The dosimetry planning software used was described by Davidson et al.[44] The interpatient variability of the PS pharmacokinetics, i.e., the PS distribution as a function of time, and variability in tissue sensitivity to WST09-VTP were suggested as potential causes for incomplete response in patients receiving high-dose PDT.

The Lund group started to consider interstitial PDT in localized prostate cancer around 2000. The group has experience of interstitial treatment of thick tumors using optical fibers (see, e.g., Refs. 45–49), and diagnostic and dosimetric capability was being developed. The first interstitial treatment system involved splitting the optical power from a treatment laser into six parts delivered through six individual fibers, which could be inserted into the tumor mass. To gain clinical experience with this system, the first treatments were performed on easily accessible thick skin tumors. The treatment light emitted by any of the inserted fibers to any of the others, now acting as a receiver, was measured intermittently by mechanically inserting a detector in the light path while blocking the treatment beam, as shown in Fig. 4. By monitoring the amount of light passing between the fiber tips it is possible to model the light dose distribution throughout the tumor. The system was evaluated in the treatment of experimental tumors in rats,[45,46] and was later used in early treatment of solid hu-

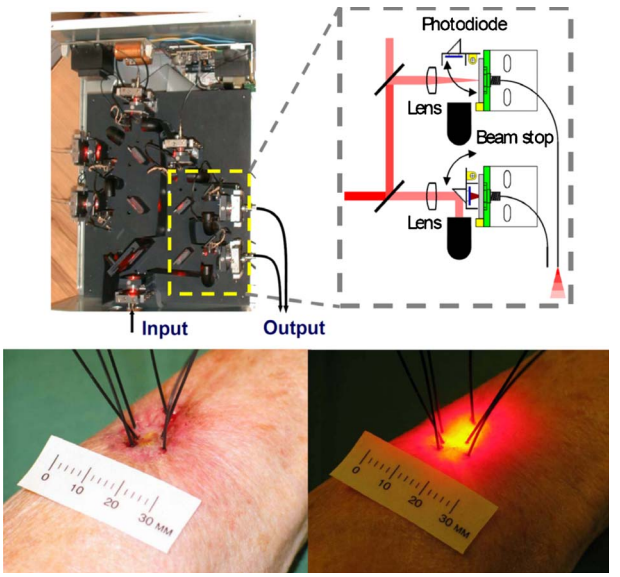

Fig. 4 Setup used for interstitial PDT of skin malignancies using a six-fiber system, where the fluence in the tissue can be measured can be measured using one fiber for transmitting light to the tissue and by inserting a detector in front of another fiber, while at the same time blocking the treatment light intended for that particular fiber. The situation when one fiber emits treatment light and the other five are measuring the emitted light is shown in the lower left part of the figure, while the situation when all six fibers are transmitting treatment light is shown in the lower right part.

man tumors.[47–49] Photographs from a treatment session are included in Fig. 4.

To design dosimetry models to account for the actual levels of PS and oxygen in the different parts of a tumor, a new approach was adopted; first described in Refs. 47–49. A mechanical switch-yard system was invented enabling all the fibers to be used as transmitters for therapeutic as well as diagnostic radiation, and as receivers for diagnostic information on therapeutic light fluence, tumor sensitizer, and oxygen levels. The basic elements of the technique are presented in Fig. 5 for the case of six interstitial fibers. Individually adjustable diode lasers were used to supply light to each of the treatment fibers. Photographs from a treatment session of a solid skin tumor on the ear are included in Fig. 5.

Clearly, a system of the kind just described can be fully utilized only in conjunction with advanced dosimetric software, where measured diagnostic signals are fed into a dose distribution calculation program.[48,50–52] In general, the approach taken is to rely on the "threshold dose" concept.[53,54] This means ensuring that a minimum dose, i.e., that required to induce direct cell death, is received by all parts of the target volume, as schematically depicted in Fig. 6, which shows the case for prostate cancer treatment with an 18-fiber system. In practice, the dose can be defined in several ways. Taking the light distribution, i.e., the fluence rate Φ, and the photosensi-

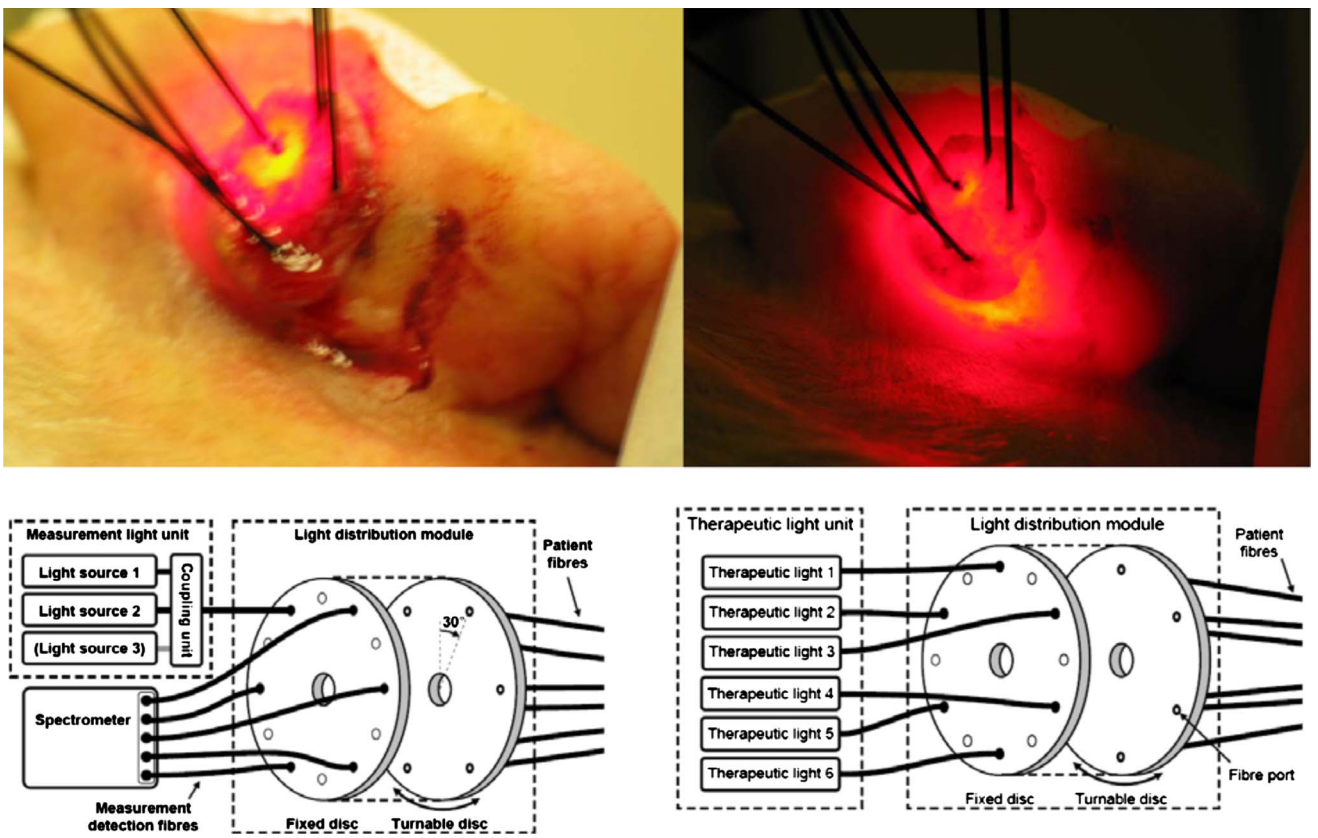

Fig. 5 Schematic views of a six-fiber system with diagnostic capability (light fluence, sensitizer concentration, and tissue oxygenation) and treatment capability. The diagnostic situation is shown on the left with one fiber used as a sender and the rest as receivers, and the treatment situation on the right with all fibers used to illuminate light. In the upper part of the figure a solid tumor is shown. (Diagrams showing fiber arrangement schemes are from Ref. 47.)

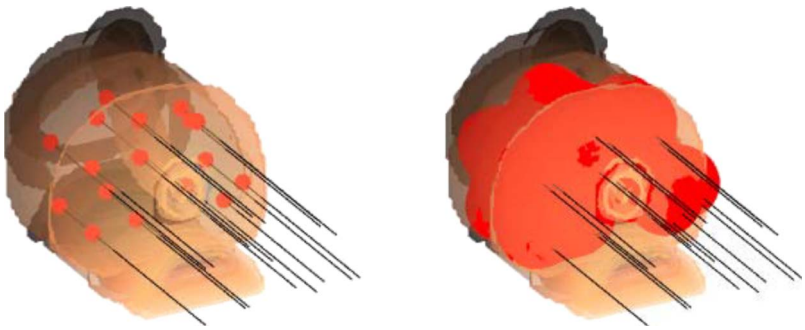

Fig. 6 Illustration of calculated treatment light fluence being delivered through multiple optical fibers positioned inside the prostate gland: (a) and (b) show two different instances during the same treatment session, where the isosurfaces indicate tissue that has received at least the threshold dose.

tizer concentration [PS] into account, the PDT dose is defined by

$$D_{\mathrm{PDT}} = \int_0^T \varepsilon[PS]\Phi \, \mathrm{d}t, \tag{1}$$

where ε is the extinction coefficient of the PS, and T is the treatment time. In the interstitial setting, D_{PDT} should exceed the threshold value throughout the target volume. This means that [PS] and Φ must be quantified in three dimensions. In a simplified version, it is assumed that the sensitizer is distributed homogeneously throughout the target volume. This is referred to here as the fluence dose, and is defined by

$$D_{\mathrm{Fluence}} = \int_0^T \Phi \, \mathrm{d}t. \tag{2}$$

The fluence rate can be assessed using calibrated optical probes, where integrating the signal over the treatment time yields the fluence dose.[55,56] Such point measurements are valuable for providing representative values of the light dose delivered at one location. To obtain a spatial map of the fluence rate throughout the entire target volume, the photon propagation must be theoretically calculated. The optical properties of the tissue treated are then determined, followed by calculations using a photon propagation model. One example of a theoretical model is the analytical solution to the diffusion equation, i.e.,

$$\Phi(r) = \frac{P}{4\pi D r} \exp(-\mu_{\mathrm{eff}} r). \tag{3}$$

Here P (in watts) is the source power, D (in centimeters) is the diffusion coefficient, μ_{eff} (in inverse centimeters) is the effective attenuation coefficient of the light in the treated tissue, and r (in centimeters) is the radial distance from the point source.

In interstitial PDT, the optical properties are typically evaluated through steady state, spatially resolved protocols,[35,42,52,57] where homogeneous distribution of absorption and scattering is assumed. Recently, heterogeneous models have been reported utilizing tomographic measurement schemes. Wang and Zhu used a translatable detector fiber in the prostate collecting light at different distances from a steady state light source.[58] Several studies have been carried out in which the optical fibers delivering and collecting the light were placed transrectally. The optical properties are then reconstructed using structural information obtained from prior ultrasound examinations[59,60] or MRI (Ref. 61).

Following the evaluation of the optical properties, the theoretical model yields the fluence rate throughout the treated tissue. A wide variety of models have been developed in interstitial PDT dosimetry. For example, accelerated Monte-Carlo methods,[62] higher order approximations of the radiative transport equation,[63,64] finite element methods,[44] and homogeneous models[52,65] of the diffusion equation, i.e., Eq. (3).

The calculation of fluence rate at every point within the target volume is inherently connected to pretreatment planning. The problem is to tailor the light distribution so that the whole target volume receives a fluence dose above the threshold. In addition to the treatment time, other parameters that must be optimized are the positions, shape and power of the light sources.[39,44,51,52,65,66]

Most groups utilize optical fiber diffusers to deliver the treatment light, while the Lund rationale is to adopt bare-end optical fibers. Bare-end fibers allow well-defined positions when using them as sources or detectors, and thus provide a well-defined source-detector distance in any measurements conducted with the fibers. More accurate values of the optical properties of the tissue can thus be obtained with such fibers. Dosimetry software has been developed to calculate the optimum positioning of the fibers based on the geometry of the tumor and the organs at risk. Predefined values for absorption and scattering can be assigned to different types of tissue. The irradiation times for the individual fibers can then be calculated. The aim of this calculation is to maximize the fluence dose to the prostate gland, while minimizing the dose to the organs at risk. In addition to the pretreatment planning, the instrument developed in Lund performs dosimetry calculations during treatment. In this way, the irradiation times can be updated based on treatment-induced changes in the optical properties. The general procedure is described in Refs. 52 and 67.

A clinical trial using an 18-fiber interstitial PDT system, constructed together with SpectraCure AB (Lund, Sweden)

Fig. 7 Photographs taken from a treatment session of prostate cancer with an 18-fiber system for interstitial PDT with integrated dosimetry feedback functions. The top left photo illustrates the treatment system, while the top right photo shows the ultrasound image from which the prostate gland is delineated and fiber positions measured. The photos in the lower row present fiber positioning, treatment light irradiation, and prostate gland delineation situations, respectively. (Courtesy of SpectraCure AB.)

along the principles developed by the Lund University group, has so far comprised four prostate cancer patients. The system, procedures, and clinical outcome of these activities have been described previously.[68] Photographs from the clinical procedures are shown in Fig. 7. The optimum positions of the fibers were calculated based on colorectal ultrasound imagery, and irradiation was performed with interruption for dosimetry data collection. The laser light fluence rate through the tumor mass was measured regularly and used to recalculate the optimum light delivery based on the threshold doses set for the treated target tissue and organs at risk in the vicinity of the target tissue. The sensitizer concentration and level of oxygenation were also monitored, but the data were not used to influence the treatment procedure. Incorporation of these data should help to achieve optimized, individual treatment.

The dosimetry algorithms reported to date rely on the fluence dose, i.e., Eq. (2), but as already mentioned, to refine the dose calculations the sensitizer concentration should also be quantified. Several preclinical studies have reported less variation in PDT response when compensating for varying levels of sensitizer in the target medium.[69,70]

Photosensitizer concentration can be assessed through absorption[42] or fluorescence[36] point measurements. We used fluorescence data. The drug uptake in the target volume can vary between individuals as well as within each individual. Hence, analogously to the fluence rate calculations, the sensitizer distribution must be assessed in three dimensions. This led to the need for tomographic reconstruction of the PS concentration throughout the medium. A method of doing this was presented previously.[71]

Interstitial PDT for the treatment of prostate cancer is being continuously developed. Several groups have stressed the need for more sophisticated dose-planning approaches. Many aspects must be considered, such as individual variations in blood supply to the gland, type of PS, concentration and localization of PS, the oxygen concentration in and optical properties of the gland, and the size and pathology of the prostate gland. Risk organs in the close vicinity of the prostate must also be considered, e.g., the bladder, to avoid the risk of incontinence. In addition, the general health status of the patient, the treatment time, and light sensitivity of the patient during and following treatment must be considered. Still, this new modality for prostate cancer therapy is thus very promising. Protocols and instrumentation capable of such dosimetry are available and already in use in several clinical trials, but the precise dosimetry algorithms, intricate in nature, have yet to be defined.

8 Discussion

PDT is gaining increased acceptance in the management of malignant disease. Its minimally invasive nature combined with the possibility of retreatment are attractive features of this treatment modality. A serious drawback of the technique is that many sensitizers cause prolonged light sensitivity of the skin, requiring discipline among patients to avoid being exposed to strong ambient light for periods that could last a month. This is not the case when using ALA-induced PpIX sensitization, which is especially useful in the management of nonmelanoma skin cancer, and is thus widely applied.

Interstitial PDT of deep-lying lesions requires detailed and individualized dosimetry, taking spatially resolved light fluence, sensitizer concentration, and level of tissue oxygenation into account in order to achieve the full advantages of the modality. Several groups, including ours, are addressing this challenge. PDT would gain considerable benefit from the development of improved sensitizers with high tumor specificity, high quantum efficiency, long-wavelength activation, and fast skin clearance. Extensive efforts are being made in this direction, including the development of functionalized nanoparticles.

The optimzation of PDT is a particularly multidisciplinary task requiring close collaboration between medical specialists in different fields, physicists, and biochemists. PDT could offer the prospect of cure for patients with various malignant pathologies. Being minimally invasive and requiring limited infrastructure, this treatment modality could also prove particularly useful in third-world countries where health-care resources are limited.

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